## Remarks

Claims 2, 3, 5-9, 13, 15, 17, 19 and 21 are pending in the application. Claims 2, 3, 5, 9, 13 and 15 have been amended. Support for amended claims 2 and 3 is found on pg. 42, lns. 8-22 of the specification. Support for amended claim 5 is found on pg. 32, lns. 14-32 of the specification. Support for amended claim 9 is found on pg. 3, ln. 17. Support for amended claims 13 and 15 is found on pg. 39, ln. 35 to pg. 40, ln. 5.

Based on the above changes and the following remarks, reconsideration of the claims is requested.

Response to section 112, 2nd paragraph rejections

Claims 2 and 3, and their dependent claims 5-9, are rejected under 35 U.S.C. 112, 2nd paragraph as being indefinite for reciting "an exon 5 coding region," as the Examiner alleges that there can be only one exon 5 in a gene. In order to more clearly define the invention, claims 2 and 3 have been amended to recite that the stop codon is "in exon 5." The scope of claims 2, 3 and 5-9 has not been altered by this amendment.

Claims 13 and 15, and claims 17, 19 and 21 (which depend from claim 15) are rejected under 35 U.S.C. 112, 2nd paragraph as being indefinite for allegedly not indicating that tumor formation rate in transgenic mice is determined relative to the tumor formation rate in control mice. These claims have been amended to more clearly indicate that the tumor formation rate in the transgenic mice is determined relative to the control animals. The scope of claims 13 and 15, and claims 17, 19 and 21 has not been altered by this amendment.

Claim 5, which depends from claim 2, is rejected under 35 U.S.C. 112, 2nd paragraph as allegedly being indefinite for reciting that the FHIT gene disruption is in both the germline and somatic cells. Claim 2 specifies that the transgenic mouse carries the FHIT gene disruption in its genome. The examiner believes that "genome" in claim 2 encompasses the genetic complement of each cell in the claimed mouse, and thus claim 2 already encompasses transgenic mice in which both the somatic and germline cells have

an FHIT disruption. According to the Examiner, Claim 5 therefore does not further limit claim 2.

Claim 5 has been amended to depend from claim 3, which recites a *chimeric* transgenic mouse. In a chimeric transgenic mouse, not all cells carry a FHIT gene disruption. Claim 5 therefore does further limit claim 3, as claim 5 specifies that the chimeric transgenic mouse carries the FHIT gene disruption in somatic cells and in germline cells.

The amendments discussed above render claims 2, 3, 5-9, 13, 15, 17, 19 and 21 clear and definite, and Applicants respectfully request that the 35 U.S.C. 112, 2nd paragraph rejections be withdrawn.

Response to the section 112, 1st paragraph rejections

Claims 2, 3, 5-9, 13, 15, 17, 19 and 21 are rejected under 35 U.S.C. 112, 1st paragraph as allegedly being non-enabled for a transgenic mouse with a disruption in any FHIT gene, for "comparing the mice as broadly claimed," or for a transgenic mouse with a homozygous disruption in the FHIT gene. Applicants respectfully traverse these rejections.

The Examiner alleges that claims 2 and 3 encompass transgenic mice with disruptions in FHIT genes other than the one FHIT gene identified in the art or taught in the present specification. Without admitting the propriety of the rejection, claims 2 and 3 have been amended to recite that the transgenic mice carry "a FHIT gene disruption." Applicants believe that these amendments should obviate the Examiner's concern that the claims encompass disruptions in multiple FHIT genes.

According to the Examiner, claims 13 and 15 do not specify that the rate of tumor formation in test animals is compared to the tumor formation rate in control animals. Thus, one skilled in the art would allegedly not be able to determine, respectively, which molecules are carcinogenic or which molecules have therapeutic efficacy by practicing the claimed methods. The comparison step of claims 13 and 15 has been amended to

specify that the rate of tumor formation in transgenic mice following administration of the test molecule is compared to the rate of tumor formation in control mice that have not received the test compound.

The Examiner also alleges that claims 2, 3, 5-9, 13, 15, 17, 19 and 21 are not enabled for heterozygous FHIT -/- mice that have increased susceptibility to visceral and sebaceous tumors, or display increased tumor formation upon being exposed to N-nitrosomethylbenzlamine ("NMBA"), relative to FHIT +/+ mice. According to the Examiner, one skilled in the art would be unable to predict that FHIT -/- mice would have the claimed phenotype, because this phenotype was not directly demonstrated in the present specification.

The test of enablement is whether one reasonably skilled in the art could make or use the claimed invention from the teachings of the specification, coupled with information known in the art, without undue experimentation. *See* M.P.E.P. 2164.01. In the "unpredictable" arts such as chemistry and biotechnology, some experimentation may be required to identify compounds and methods which fall within the scope of the claims. However, as long as the experimentation does not "require ingenuity beyond that to be expected of one of ordinary skill in the art," the experimentation will not be undue. In re Angstadt, 190 U.S.P.Q 214, 218 (CCPA 1976), citing Fields v. Conover, 170 U.S.P.Q 276, 279 (1971). For example, following specific directions provided in the specification (*e.g.*, detailed working examples) generally does not constitute "undue experimentation." See In re Wands, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) and M.P.E.P. 2164.06(b).

Here, one skilled in the art would have believed, from the teachings of the specification and from their general knowledge, that FHIT -/- mice would have the claimed phenotype. For example, Figs. 3B-F show that squamous papillomas and other tumors (especially sebaceous tumors) in the heterozygous FHIT +/- mice are FHIT negative. The FHIT protein was also inactivated in NMBA-induced tumors from heterozygous FHIT +/- mice, although only one FHIT allele carried an inactivating mutation (see Example 6.3, pg. 46, lns. 17-35). As stated in the specification at pg. 50,

lns. 21-14, the FHIT protein therefore appears to be a "gatekeeper" tumor suppressor, the absence of which causes a tumorigenic phenotype. Because the FHIT -/- mice are viable and long-lived, one skilled in the art would expect the homozygous knockout mice to exhibit a tumorigenic phenotype which is similar to the heterozygous knockout mice.

In any case, no more than routine experimentation is needed to confirm that homozygous FHIT -/- mice have the claimed tumorigenic phenotype. The Applicants have demonstrated that the FHIT -/- mice can be successfully made by following the teachings of the present specification; see section 5.8 beginning on pg. 32, sections 5.10 and 5.11 beginning on pg. 34, and Example 6.2 on pg. 44, lns. 19-26. The phenotype of these mice can be confirmed by simply following the protocols set forth in the working examples; see especially pg. 42, lns. 8-22 and pg. 44, ln. 35 to pg. 46, ln. 13.

The experiments outlined in the specification for determining the phenotype of the FHIT -/- mice were in fact carried out, and are reported in Zanesi et al. (2001), *P.N.A.S USA* 98: 10250-10255 (copy attached). The Applicants are co-authors of Zanesi et al.

As shown in Zanesi et al., both FHIT +/- and FHIT -/- mice exhibit increased susceptibility to spontaneous and induced tumor formation, as compared with control wild-type FHIT +/+ mice. According to the authors, "[f]or both spontaneous and induced tumors, the frequency of tumor development was not significantly different in the *Fhit*-deficient mice of the +/- and -/- genotypes, suggesting that loss of one *Fhit* allele had nearly the same effect on tumor development as loss of both *Fhit* alleles[.]" See pg. 10250, 2nd col. of Zanesi et al.

Zanesi et al. determined the rate of spontaneous tumor formation in various tissues of the transgenic and control mice over a period of two years, as described on pg. 42, lns. 15-22 of the present specification. (In the present specification, the mice were sacrificed at 54-59 weeks.) Zanesi et al. report that spontaneous tumor formation among FHIT -/- and FHIT +/- mice was six-fold higher than in wild-type control mice, and the incidence of tumors per mouse was 10-fold higher in FHIT-deficient individuals than in

wild-type littermates. The FHIT-deficient mice also had a high incidence of sebaceous and visceral tumors. See Zanesi et al., pg. 10254, 1st col., and Tables 2 and 3.

Zanesi et al. determined the rate of induced tumor formation in the transgenic and control mice by feeding the mice eight intragastric doses of N-nitrosomethylbenzlamine ("NMBA") and evaluating esophageal, stomach and other tissues, exactly as described on pg. 46, lns. 8-22 and pg. 44, ln. 35 to pg. 46, ln. 13 of the present specification. According to Zanesi et al., 100% of FHIT -/- and FHIT +/- mice developed tumors of the esophagus, forestomach and squamocolumnar junction, while only 25% of the control FHIT +/+ mice developed such tumors. See Zanesi et al., the passage bridging the 1st and 2nd cols. of pg. 10253.

Zanesi et al. performed a second experiment to determine the rate of induced tumor formation in FHIT-deficient vs. control mice, in which the mice were fed one intragastric dose of NMBA. The mice were sacrificed 29 weeks later, and tissues were examined as for the eight-dose NMBA experiment. Zanesi et al. report that 78% of FHIT +/- mice and 89% of FHIT -/- mice developed tumors after one dose of NMBA, as compared to about 8% of control mice. Also, induced tumor formation among FHIT -/- and FHIT +/- mice was 12 to 16-fold higher than in wild-type control mice, and the incidence of gastric tumors per mouse was ten-fold higher in FHIT-deficient individuals than in wild-type littermates. According to Zanesi et al., "the trend toward more tumors in Fhit -/- relative to Fhit +/- mice was not statistically significant at this NMBA dose and time of observation." See the passage bridging pgs. 10253 and 10254 of Zanesi et al.

Thus, Zanesi et al. confirm that FHIT -/- mice, which are made according to the exact protocol disclosed in the present specification, have increased susceptibility to visceral and sebaceous tumors or display increased tumor formation upon being exposed to NMBA, relative to FHIT +/+ mice. The FHIT -/- phenotype was confirmed by Zanesi et al. with protocols which were identical, or nearly identical, to those set forth in the present specification. Therefore, the present specification provides sufficient guidance to

allow one skilled in the art to make a transgenic FHIT -/- mouse with the phenotype recited in claims 2 and 3, without undue experimentation.

Claims 2, 3, 5-9, 13, 15, 17, 19 and 21 are believed to be enabled, and Applicants respectfully request that the 35 U.S.C. 112, 1st paragraph rejection of these claims be withdrawn.

Conclusion

Based on the foregoing, Applicants believe that all pending claims are in condition for allowance. An early and favorable action in this regard is earnestly solicited.

Respectfully submitted,

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